

REVIEW ARTICLE

A four-country comparison of healthcare systems, implementation of diagnostic criteria, and treatment availability for functional gastrointestinal disorders

A report of the Rome Foundation Working Team on cross-cultural, multinational research

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Key Messages

- This report identified seven key issues related to healthcare provision that may impact how patients with FGIDs are investigated, diagnosed and managed.
- Variations in healthcare provision around the world in patients with FGIDs have not been reviewed.
- We compared four countries that are geographically and culturally diverse, and exhibit differences in the healthcare coverage provided to their population: Italy, South Korea, India and Mexico.
- Since there is a paucity of publications relating to the issues covered in this report, some of the findings are based on the authors' personal perspectives, press reports and other published sources.
- Future directions for conducting cross-cultural and multinational research in FGIDs are provided.

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Abstract

Background Variations in healthcare provision around the world may impact how patients with functional gastrointestinal disorder (FGIDs) are investigated, diagnosed, and treated. However, these differences have not been reviewed. **Purposes** The Multinational Working Team of the Rome Foundation, established to make recommendations on the

conduct of multinational, cross-cultural research in FGIDs, identified seven key issues that are analyzed herein: (i) coverage afforded by different healthcare systems/providers; (ii) level of the healthcare system where patients with FGIDs are treated; (iii) extent/types of diagnostic procedures typically undertaken to diagnose FGIDs; (iv) physicians' familiarity with and implementation of the Rome diagnostic criteria in clinical practice; (v) range of medications approved for FGIDs and approval process for new agents; (vi) costs involved in treating FGIDs; and (vii) prevalence and role of complementary/alternative medicine (CAM) for FGIDs. Because it was not feasible to survey all countries around the world, we compared a selected number of countries based on their geographical and ethno-cultural diversity. Thus, we included Italy and South Korea as representative of nations with broad-based coverage of healthcare in the population and India and Mexico as newly industrialized countries where there may be limited provision of healthcare for substantial segments of the population. In light of the paucity of formal publications on these issues, we included additional sources from the medical literature as well as perspectives provided by local experts and the media. Finally, we provide future directions on healthcare issues that should be taken into account and implemented when conducting cross-cultural and multinational research in FGIDs.

Keywords available medications, CAM, cross-cultural, multinational trials, diagnostic procedures, expenditures, Functional gastrointestinal disorders, healthcare coverage, IBS, registration process.

Abbreviations: BM, Bowel movements; BRICS, Brazil, Russia, India, China, and South Africa (Emerging economies); BSS, Bristol Stool Scale; CAM, Complementary and Alternative Medicine; COFEPRIS, Federal Commission for the Protection Against Sanitary Risks (Mexico); EKG, Electrocardiogram; EMEA, European Medicines Agency; EU, European Union; FGIDs, Functional Gastrointestinal Disorder; GERD, Gastro-esophageal Reflux Disease; GI, Gastrointestinal; GPs, General Practitioners; H₂, Histamine 2 receptors; IBS-C, IBS with Constipation; IBS-D, IBS with Diarrhea; IBS, Irritable Bowel Syndrome; IBS-M, Mixed IBS; IMSS, Mexican Institute of Social Security (Mexico); KFDA, Korean Food & Drug Administration; MISTs, Mexico, Indonesia, South Korea, and Turkey (Emerging economies); NHI, National Health Care Insurance System (South Korea); NHS, National Health Service (Italy); PPIs, Proton Pump Inhibitors; RIIIAQ, Rome III Adult Questionnaire; USD, United States Dollars.

INTRODUCTION

The structure of healthcare services may impact the way that patients with functional gastrointestinal disorders (FGIDs) are evaluated, diagnosed, and treated. Currently there is no information available on differences in these services around the globe. The World Health Organization has ranked the performance of its 191 world members based on several indicators including: (i) improving health status and reduced health inequalities, (ii) level of responsiveness to the population's expectations, (iii) inequalities in responsiveness and fairness in financial contributions.¹ Based on these indicators, they concluded that countries with a history of civil conflict or a high prevalence of HIV and AIDS are less efficient in providing healthcare to their populations, and performance increases with higher health expenditure per capita.² However, countries may give different weights to these indicators,³ as people in different cultural and social settings value individual healthcare goals in different ways. For example, some countries may assign greater importance to indicators of health distribution and less importance to health level, so flexibility is needed when weighing the importance of each health indicator.⁴

Svoronos and Mate proposed that evaluations of public health programs should not only assess whether an intervention works, but also why and how it works. Thus, when implementing interventions which aim to improve healthcare delivery across varied populations, it is important to be sensitive to contextual differences.⁵ For example, the availability of medicines may differ across different populations and may vary from the public to the private sector within individual countries. Cameron *et al.* showed that medicines for chronic conditions (e.g., diabetes, hypertension) are less available than for acute ones (e.g., viral/parasitic infections) in low and middle-income countries, particularly in the public sector.⁶

Functional gastrointestinal disorders, especially irritable bowel syndrome (IBS) and functional constipation, are common chronic disorders^{7,8} that produce a negative economic burden because of the cost of investigations, medical consultations and surgeries that are not medically indicated, absenteeism and loss of work productivity, and impaired health-related quality of life.^{9–11} FGIDs have not been investigated as public healthcare problems, especially, from a multinational, cross-cultural perspective.⁶

As part of a comprehensive global initiative of the Rome Foundation, the Working Team on

Cross-Cultural, Multinational Research was created in June 2011 to foster multinational research in FGIDs and make recommendations on the conduct of this investigation. The Working Team was divided into five sub-committees (reported elsewhere),¹² one of which focused on Healthcare Systems and Infrastructure in Different Countries. Seven healthcare issues that need to be considered when conducting multinational, cross-cultural research in FGIDs were selected by the members of this sub-committee based on their expertise, following face to face discussions that took place in May 2012 in San Diego, California and were further distilled in a subsequent conference call with additional discussions by e-mail. Focusing especially on IBS, the most widely studied FGID, these issues are addressed in this article, and include: (i) the percentage of the population covered by the different systems/providers (i.e., national coverage, private practice); (ii) level in the healthcare system that patients are cared for (i.e., primary, tertiary care);

(iii) diagnostic procedures that are used and to what extent; (iv) knowledge and use of the Rome diagnostic criteria among healthcare providers; (v) available medications for FGIDs and the process for the registration and approval of new pharmaceuticals; (vi) the economic burden on healthcare services from FGIDs; and (vii) use of complementary and alternative medicine (CAM) for FGIDs (Fig. 1).

As it would not be feasible to conduct a comparative review of every country in the world, due to the lack of global information, we decided to compare a selected group of geographically and ethno-culturally diverse countries that would allow us to contrast healthcare provision and expectations between developed and developing economies. In this way, we wished to demonstrate the impact that these previously unrecognized parameters may have in multinational cross-cultural studies. Thus, we decided on Italy, South Korea, India, and Mexico. Both Italy and South Korea are industrialized economies with broad-based

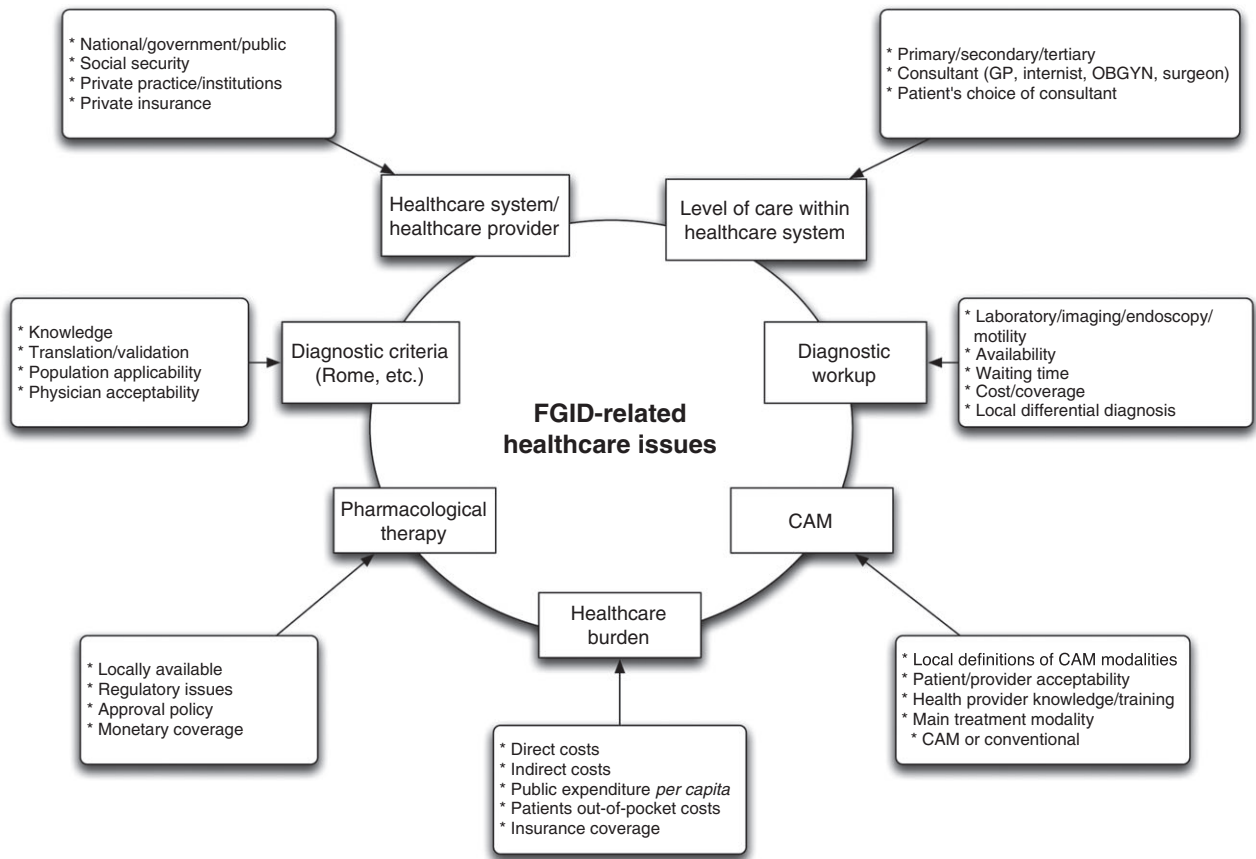


Figure 1 Healthcare issues that need to be considered when conducting multinational, cross-cultural research in FGIDs. The figure summarizes the healthcare issues related to FGIDs that have been identified by the Multinational Working Team of the Rome Foundation that need to be considered when conducting multinational, cross-cultural research in FGIDs. There is no hierarchy to these issues; rather, they are all interrelated. Factors associated with each issue are also depicted.

population-wide healthcare coverage. Italy also served as a healthcare model where there is a strong primary care service, whereas, in South Korea, healthcare is largely provided by specialists. In contrast, India and Mexico served as examples of developing, newly industrialized countries where there may be limited healthcare provision for substantial segments of the population. India is a leading emerging economy under the so-called BRICS (Brazil, Russia, India, China, and South Africa),¹³ while Mexico and South Korea are emerging fast-track markets belonging to the MISTs (Mexico, Indonesia, South Korea, and Turkey),¹⁴ which were the four largest markets in the Goldman Sachs N-11 Equity Fund, with economies that more than doubled in size over the past decade.¹⁵

Because there is a paucity of publications relating to the issues covered in this report, some of the findings are based on the authors' personal perspectives, press reports, and other non-traditional published sources. Full documentary support could not be cited in all cases. Where findings could be documented, this is indicated, with references. Four recognized researchers in FGIDs (EC, UCG, MS, SM) working in these four countries gathered all relevant available information. Results for each country are sequentially reported. At the end, future directions about healthcare issues with regard to the conduct of cross-cultural studies in FGIDs are listed.

WHICH POPULATION SECTORS ARE COVERED BY THE DIFFERENT HEALTHCARE SYSTEMS AND HEALTHCARE PROVIDERS, AND TO WHAT EXTENT?

In Italy, there is universal and free healthcare service, *Servizio Sanitario Nazionale* (National Health Service: NHS), for all residents of the European Union (EU; Table 1). This insurance covers consultations, diagnostic investigations, and treatment. There are also private practice and private insurance systems available as an alternative or supplement to the NHS.

In South Korea, healthcare is provided by the National Health Care Insurance (NHI), which has broadened its coverage since 1977 when the government first launched it, from 8.8% to almost 97% of the population in 2011.¹⁶ However, only 6.5% of physicians and 28.3% of the general public, expressed satisfaction with the NHI.¹⁶

In India, according to the constitution, the state is responsible for providing healthcare to its citizens. Over 72% of the population lives in rural areas and the government's primary healthcare system is available to this population as an open access system. However,

because of insufficient resources, manpower, and infrastructure, the government is unable to properly serve all of this population. Hence, those who can afford it often choose private institutions; the main source of healthcare for the majority of households both in urban and rural areas (63–70%).¹⁷ In addition, patients can consult government or private hospitals, both by open access or referral. Close to 80% of the urban areas have specialized health care facilities compared to 24% of the rural ones,¹⁷ and in the private sector, around 75% of the medical staff have some level of specialty training and facilities are equipped with higher technological resources than government hospitals.

In Mexico, in theory, 96–97% of the population has healthcare coverage,^{18–21} although the quality of care varies significantly across systems. The Mexican healthcare model divides the population into the 'insured' sector, referring to those who are covered by a social security system and the 'uninsured' sector that includes middle and high socioeconomic class employees who go to private practice for medical consultation and cover their healthcare expenses with out-of-pocket resources or with private insurances. A second uninsured group is comprised of very low income people who are supposedly covered by the so-called Popular Insurance that was created by the government to provide healthcare for the entire population.²¹ In addition, people are free to consult with private practice and they can go directly to a specialist with a problem that would normally be managed by general practitioners (GPs) (Table 1).

AT WHAT LEVEL OF THE HEALTHCARE SYSTEM ARE PATIENTS WITH FGIDS CARED FOR?

In Italy, GPs care for 90% of FGID patients (E. Corazziari, personal communication). However, the patient–GP ratio for adults is 1500 : 1 in the NHS (E. Corazziari, personal communication), and as a result, GPs have limited time for patient consultations. In 2009, data from 1000 GPs throughout the country indicated that patients with abdominal pain and FGIDs comprised 21.4% of consultations. Of these, 13.3% were classified as abdominal pain of unknown origin and 4.1% as IBS.²² Another study among GPs from the province of Pisa reported that IBS represented 26.2% of new diagnoses²³ and 63.3% were referred to specialists (gastroenterologists: 23.0%, psychologists/psychiatrists: 12.2%, dieticians: 7.4%, gynecologists: 18.6% of women).²³ The reasons for referrals were: perceived need for in-depth

Table 1 Healthcare systems and population covered across Italy, South Korea, India, and Mexico

Italy (population covered: %)	South Korea (population covered: %)	India (population covered: %)	Mexico (population covered: %)
National Health System (NHS) (100%) Covers for all residents of the European Union Private practice (Alternative) 1. Out-of-pocket 2. Covered with private insurances	National Health Care Insurance System (97%) Government Coverage (3%) Covers very low income/uninsured population Private practice (None) 1. Private insurances that take expenses not covered by government systems (i.e. Cancer insurance) 2. Oriental medicine clinics	Government or public health system (27–30%) 1. Primary health center (PHC) 2. Subsidiary health center (SHC) 3. Community health center 4. Others: Sub-division hospital District hospital Specialist hospital* Academic/University Hospital* Super specialty hospital or institution [†] Other Systems 1. Government Systems (Employees of public institutions and their beneficiaries: up to 18 years old. Husbands in case of no other source of healthcare if the wife is the employee)* 2. State Employees Insurance Scheme [‡] Railway hospitals Ordnance factory hospitals Central government health scheme Army hospitals Public sector: Oil and Natural Gas Corporation [ONGC], Coal India, etc. (Cover for their own employees and to some extent provide service within the working places) 3. Private–public partnership organizations* 4. Private non-profit organizations*: Christian Missionary Hospitals Other Non-Government (NGO) Systems Private practice (70% of urban, 63% rural population) 1. Community practitioners 2. Private hospitals and nursing homes 3. Corporate hospitals and private medical schools* 4. Alternative medicine systems: Allopathy Ayurveda Homeopathy	Popular Insurance (40%) Covers the ‘uninsured’ population (mainly very low income population) Hospitals of the Secretariat of Health Social Security Systems (53%) 1. Mexican Institute of Social Security (IMSS: <i>Instituto Mexicano del Seguro Social</i>) a. Obligatory Regime (Beneficiaries: Affiliated employees and their relatives) First Level: Family Medicine Units Second Level: Regional General Hospitals Third Level: Specialty Hospitals b. Opportunities Program (Native and marginalized population) 2. Institute of Social Security of State Workers (ISSSTE: <i>Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado</i>): Provider for the government employees, those in the educational sector and bureaucrats. First Level Second Level Third Level 3. Others: Mexican Petroleum Company (PEMEX: <i>Petroleos Mexicanos</i>) Army and marine Forces (SEDENA: <i>Secretaría de la Defensa Nacional</i>) Others Private practice (3%) 1. Out-of-pocket 2. Private insurances 3. Others

*In India these are Multilevel Hospitals, meaning that they provide Primary, Secondary and Tertiary healthcare. [†]Tertiary Care Hospitals, mainly provide Tertiary care. [‡]May provide Tertiary care mainly depending upon the level of the hospital.

investigation, need for reassurance, patient request, and therapeutic failure.²³

In South Korea, one study reported that 78.3% of IBS patients consulted at the primary care level, while 15.2% turned to referral centers. IBS represented $4.2 \pm 10.4\%$ of all consultations in primary care, $3.2 \pm 3.4\%$ in secondary, and $3.3 \pm 3.4\%$ in tertiary care; only 1.9% were hospitalized.^{24,25} However, the proportion of insurance claims related to IBS is similar in primary care and referral centers (0.87% vs 1.02%). Specialists rather than GPs provide primary care service which may have an impact on endoscopy and other specialist-based treatments, thus explaining the

lack of differences in insurance claims according to level of care.

In India, there are data on the frequency of consultations for gastrointestinal (GI) symptoms, but none regarding the level within the healthcare system that patients with FGIDs are cared for. In one study among 2549 community adults, in Mumbai, recruited over a 1-year period, consultation rates were 24.1% for subjects diagnosed with dyspepsia, 40.9% for those with both dyspepsia and IBS, and 10% for those with IBS alone, compared to 0.1% for subjects without any FGID.²⁶ In a nationwide study, 70% of 2785 patients with chronic lower GI symptoms presumed to have IBS,

had previously sought consultation for their symptoms compared to 12% of 4500 subjects from the community. Consultations for IBS were less frequent among individuals from rural than urban areas, and in low (18–22%) vs middle and high socioeconomic class (67–78%), suggesting that more affluent patients may have better access to healthcare.²⁷

In Mexico, according to the Mexican Institute of Social Security (IMSS), the majority of patients with IBS consult at family medicine units. In fact, a study among patients consulting at one of these units in central Mexico reported that 35% of patients between 20 and 49 years of age who attended, were diagnosed as IBS.²⁸ Only 31% had previously sought medical care for this reason (92% women) and those who had done so were slightly, but significantly, older than those who did not.²⁹ The waiting list for patients referred to the second level of care (regional hospitals) is often very long and in some centers there are no attending gastroenterologists. In these cases, patients are referred to tertiary care centers where diagnostic procedures are performed. In addition, availability of pharmacological treatments for FGIDs may be limited in the public system; so many patients go to private practice for consultation and medicine. In the Institute of Security and Social Services for the State Workers (ISSSTE), also a social security system, 50% of consultations to gastroenterology clinics are because of IBS and 70% of the patients are women as well.³⁰ In private practice, IBS is the main reason for consultation with gastroenterologists and among the 14 most common reasons for consultation in general.³¹

KNOWLEDGE AND USE OF THE ROME DIAGNOSTIC CRITERIA

Italian GPs do not routinely use the Rome criteria, although many of them know of their existence

(Table 2). In the study from Pisa, only 35.7% of 28 physicians that were surveyed stated that they were familiar with the Rome II criteria and 21.4% used them in their practice. They correctly detected changes in bowel habit, followed by abdominal pain, discomfort, and bloating, as the most important symptoms required for a diagnosis of IBS. However, about 20% of patients were diagnosed as IBS even though they did not report abdominal pain or discomfort.²³ Although 60.7% judged their personal knowledge of IBS to be insufficient, only 10.7% considered that further educational measures could be useful.²³

In South Korea, the Rome III adult questionnaire (RIIIAQ) has been translated based on the Rome Committee guidelines for this purpose.²⁴ Using this instrument, an investigation conducted in primary and tertiary care centers, showed a low agreement (kappa 0.08) in IBS subtyping between the RIIIAQ and the Bristol Stool Scale (BSS). The RIIIAQ classified IBS as IBS with constipation (IBS-C) in 16.6%, IBS with diarrhea (IBS-D) in 29.3%, and Mixed IBS (IBS-M) in 49.0%. In contrast, with the BSS, 24.2% reported having stools Types 1-2, 27.4% Types 6-7, and 43.9% Types 3-5. The applicability of the BSS was questioned as some patients considered BSS-Type 3 as hard stools and Type 5 as loose stools.²⁴

In India, GPs are not familiar with Rome criteria and many gastroenterologists believe that these criteria may not be applicable as pain and discomfort are absent in 30% of patients considered to have IBS.²⁷ In a multicenter study among 1618 patients who were diagnosed as IBS, based on the presence of chronic lower GI symptoms with no alarm features and negative investigations, 91.2%, 67.9%, 40.1%, and 52.5%, fulfilled three to four Manning criteria, Rome I, II, and III criteria, respectively, while 74.5% fulfilled the not yet validated Asian criteria for IBS.³² The latter include recurrent abdominal pain, bloating, or any

Table 2 Knowledge and use of Rome criteria for IBS

	Italy	South Korea	India	Mexico
Knowledge/Use by GPs	Yes/No	Yes/Limited	No/No	Yes/Limited
Knowledge/Use by Gastroenterologists	Yes/Limited	Yes/Yes	Yes/No	Yes/Yes
Limitations of Rome criteria	None	Some patients consider Bristol Type 3 as hard and Type 5 as loose stools	Absence of abdominal pain/discomfort in 30% Absence of Pain: Relief with stools/With more frequent/Loose stools No differences in stool frequency between IBS-C and IBS-D, thus stool frequency criteria cannot be used for subtyping	None
Criteria best suited	Rome III	Rome III	Manning Asian Criteria	Rome II

other discomfort for ≥ 3 months, associated with one or more of the following: relief with defecation, change in stool form (identified by the BSS), and a change in stool frequency.³³ The most common Rome criteria not fulfilled by patients meeting the Asian criteria for IBS were: 'more frequent stools with onset of pain,' 'loose stools with onset of pain,' 'relief of pain with passage of stool,' 'bloating' and in a minority, a duration of greater than 12 weeks. These findings are in agreement with data from a previous multicenter study among 2785 patients considered to have IBS based on the presence of chronic lower GI symptoms, no alarm features and negative investigations for organic causes, and 4500 asymptomatic community subjects. Abdominal pain or discomfort were frequent but not universal and, most importantly, weekly stool frequency was similar irrespective of whether the patients felt that they had constipation (median: 14, range: 0–21), or diarrhea (14, 7–35).²⁷ Only 39% of those with constipation could be so classified based on the Rome criterion of < 3 bowel movements (BM) a week, and 4.0% as diarrhea based on the presence of > 3 BM a day. Patients with self-perception of diarrhea predominance were more likely to report a sense of incomplete evacuation, while those with constipation reported using enemas more frequently.²⁷ Therefore stool consistency may be the best parameter for classifying the bowel habit subtype.³²

In Mexico, the Rome criteria are very well accepted and are considered the gold standard for diagnosing IBS,³⁴ but physicians are not familiar with the different versions. In a recent survey, 64.6% reported using the Rome III criteria to diagnose IBS, 11% Rome II, 0.8% Rome I, 23.6% their clinical experience, while no one reported using Manning criteria. However, the correct identification of Rome III criteria by those who reported using them compared to those who did not, was 72% vs 33.3% ($p < 0.05$).³⁵ Physicians in private practice were the least likely to correctly identify the different criteria followed by those working in public hospitals/social security and academics.³⁵ Both Rome II and III questionnaires have been translated and validated in Spanish-Mexico, however, the RIIIAQ seems to yield a much lower prevalence of IBS (16 vs 4.4%) with a very low agreement (38.5%) between the two instruments.³⁶ According to researchers' experience, the prevalence defined by Rome II appears to be more accurate (Table 2).

WHICH DIAGNOSTIC PROCEDURES ARE USED FOR FGIDS, AND TO WHAT EXTENT?

In Italy, 61.6% of dyspeptic patients with predominant epigastric pain and 35.0% of those with other non-pain

symptoms, who see GPs, are referred for upper GI endoscopy regardless of their age, probably related to the low cost of endoscopy.³⁷ In 1990, a study identified risk factors for organic disease in patients with colonic symptoms that would suggest the need for a diagnostic colonoscopy. These included elevated erythrocyte sedimentation rate, blood in the stools, leukocytosis, age > 45 years, slight fever, and the presence of colonic neoplasms in first-degree relatives. In contrast, visible abdominal distension, bloating, presence of IBS in first-degree relatives, flatulence, and irregularities in BM were suggestive of IBS.³⁸ In the study from Pisa, after clinical evaluation, additional tests were ordered in more than 74% of the patients, including full blood counts, fecal occult blood tests, thyroid function tests, lower GI endoscopy, barium enema, upper endoscopy, and abdominal ultrasound; independently of bowel habit predominance.²³ It is also considered important to rule out celiac disease and lactose intolerance in patients with IBS (E. Corazziari, personal communication). Manometry/pH monitoring studies are needed to rule out motility disorders and gastro-esophageal reflux disease (GERD) as well as for diagnosing functional anorectal disorders. In Italy, they are available in GI units in tertiary care centers (Table 3). The NHS provides laboratory, imaging and endoscopic procedures, motility, and pH studies. However, waiting lists for endoscopy and ultrasound can be very long, so patients who can afford it often turn to private practice or move to areas with shorter waiting periods and perceived higher standards of medical practice.³⁹

In South Korea, 55.7% of IBS patients undergo colonoscopy, 27.5% abdominal ultrasound, and 14.3% abdominal CT scan. Other investigations include upper endoscopy (53.8%), urine analysis (36.3%), sigmoidoscopy (7.3%), barium enema (7.3%), abdominal magnetic resonance imaging (1.5%), positron emission tomography-computed tomography (0.7%), and 'routine' screening tests (5.5%). The components of the latter vary between hospitals, but usually include a full blood count, blood chemistry, thyroid function tests, serum level of carcinoembryonic antigen, urine analysis, abdominal ultrasound, chest X-ray, EKG, and upper endoscopy.⁴⁰ Motility studies are available in tertiary care by referral; however, in primary and secondary care, colorectal clinics perform water perfused anorectal manometry (Table 3).

In India, the treating physician decides which diagnostic procedures are indicated and many diagnostic procedures including upper endoscopy/colonoscopy, manometry, and ultrasound are available through open access (Table 3). Waiting lists are quite short and many

Table 3 Availability and accessibility of investigations necessary to rule out gastroesophageal reflux disease and motility disorders as per Rome III criteria

	Italy		South Korea		India		Mexico	
	Availability	Accessibility	Availability	Accessibility	Availability	Accessibility	Availability	Accessibility
pH monitoring: Catheter/Bravo	Yes	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHI	Yes	Multilevel and tertiary care (by referral/ open access), PP	Yes	Tertiary care (by referral), PP
Impedance-pH	Yes	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHI	Very limited	Multilevel care-Academic (by referral/ open access)	Yes	Tertiary care (by referral), PP
Esophageal manometry: Water perfused	Yes	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHS	Yes	Multilevel and tertiary care (by referral/ open access)	Yes	Tertiary care (by referral), PP
Solid state	Very limited	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHI	Very limited	Multilevel care-Academic (by referral/ open access)	Yes	Tertiary care (by referral), PP
High resolution	Very limited	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHI	Yes	Multilevel care (by referral/ open access)	Yes	Tertiary care (by referral), PP
3D High resolution	Very Limited	Tertiary care (by referral)-NHS	No		Very limited	Tertiary and Multilevel care (by referral/ open access)	Very Limited	PP
Gastric emptying studies: Scintigraphy	Yes	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHI	Yes	Multilevel care (by referral/ open access)	Yes	Tertiary care (by referral), PP
¹³ C octanoic acid	Yes	Tertiary care (by referral)-NHS	No		No		No	
Ultrasonography	Yes	Tertiary care (by referral)-NHS	Very limited	Tertiary care (by referral)-NHI	Very limited	Multilevel care (by referral/ open access)	Very limited	PP
MRI	Yes	Tertiary care (by referral)-NHS	Research	Academic	Very limited	Multilevel care (by referral/ open access)	Very limited	PP
Colon transit: Radio-opaque markers	Yes	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)- NHI	Yes	Multilevel care (by referral/ open access) PP	Yes	Tertiary care (by referral), PP
Scintigraphy	Research	Academic	No		Very limited	Multilevel care (by referral/ open access)	No	
Anorectal manometry: Water perfused	Yes	Tertiary care (by referral)-NHS	Yes	Primary, secondary, tertiary care (by referral)-NHI	Yes	Multilevel and tertiary care (by referral/ open access)	Yes	Tertiary care (by referral), PP

Table 3 Continued

	Italy		South Korea		India		Mexico	
	Availability	Accessibility (by referral)-NHS	Availability	Accessibility (by referral)-NHI	Availability	Accessibility (by referral)-NHI	Availability	Accessibility (by referral), PP
Solid state	Yes	Tertiary care (by referral)-NHS	Yes	Primary, secondary, tertiary care (by referral)-NHI	Very limited	Multilevel care (by referral/ open access)	Yes	Tertiary care (by referral), PP
High resolution	Very limited	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)-NHI	Yes	Multilevel care (by referral/ open access)	Yes	Tertiary care (by referral), PP
3D High definition	Very limited	Tertiary care (by referral)-NHS	No		Very limited	Multilevel and tertiary care (by referral/ open access)	Research	Academic
Defecography:								
Conventional (contrast)	Yes	Tertiary care (by referral)-NHS	Yes	Tertiary care (by referral)- NHI	Yes	Multilevel care (by referral/ open access) PP	Yes	Tertiary care (by referral), PP
MRI	Yes	Tertiary care (by referral)-NHS	Very limited	Tertiary care (by referral)-NHI	Very limited	Multilevel care (by referral/ open access)	Very limited	PP
Breath tests:								
Carbohydrate intolerance	Yes	Tertiary care (by referral)-NHS	Research	Academic	Yes	Multilevel care (by referral/ open access) PP	Very limited	Tertiary care (by referral), PP
SIBO	Yes	Tertiary care (by referral)-NHS	Research	Academic	Yes	Multilevel care (by referral/ open access) PP	Very limited	Tertiary care (by referral), PP
Se ⁷⁵ HCAAT	No		No		No		No	

MRI: Magnetic Resonance Imaging. Se⁷⁵HCAAT: Selenium Homocholic Acid Taurine or Taurosecholic acid. Tertiary care (by referral): In Italy they are Gastroenterology Units within University/Academic and General Hospitals and they are covered by the NHS (National Health System); in South Korea they include University/Academic and General Hospitals; in India they include Academic/University Hospitals, Specialty and Multispecialty Hospitals and may be covered by the NHI (National Health Insurance), or Corporate Hospitals which are usually Multilevel Care Hospitals (include Primary, Secondary and Tertiary care); Mexico they include University/Academic and General Hospitals from the Secretariat of Health and Social Security Systems. Academic: Centers where the studies are conducted only for research purposes. PP: Private Practice. Patients may request the studies without a prior physicians order (However they are usually recommended by a referring physician).

Table 4 Available medications for IBS in Italy, South Korea, India, and Mexico

Medication	Italy	South Korea	India	Mexico
Fiber supplements	Psyllium (Isphagula, Plantago ovata) Glucomannan, Guar Gum (Galactomannan) Polycarbophyle calcium PHGG (Partially Hydrolyzed Guar Gum) Inulin Oligofructose Insoluble fibers: Wheat bran Lignin Cellulose Hemicellulose	Psyllium husk, Psyllium granules (Agiocur pregranules) Polycarbophyle calcium	Psyllium (Ispaghula husk) Polycarbophyle calcium	Psyllium (Isphagula, Plantago ovata) Polycarbophyle calcium
Osmotic Laxatives	Lactulose Lactitol Sorbitol Mannitol Macrogol, Polyethylenglycol	Magnesium hydroxide Lactulose Lactitol Macrogol, Polyethylenglycol	Magnesium hydroxide Lactulose Lactitol Sorbitol Macrogol, Polyethylenglycol	Magnesium hydroxide Magnesium chloride Lactulose Lactose Lactulose (with Paraffin) Macrogol, Polyethylenglycol Docusate sodium
Emollients				Bysacodyl
Stimulant/Irritative Laxatives	Bysacodyl Cascara Dantron Senna Sodium picosulphate	Bysacodyl	Bysacodyl Sodium picosulphate	Bysacodyl Cassia acutifolia Fenolfalein Sennosides A-B
Secretory agents Prokinetics	Linaclotide Clebopride Domperidone Levolsulpiride Metoclopramide Prucalopride	Clebopride Domperidone Misoprostol Mosapride	Lubiprostone Cinitapride Domperidone Itopride Levolsulpiride Metoclopramide Mosapride	Linaclotide Cinitapride Domperidone Itopride Levolsulpiride Metoclopramide Misoprostol Mosapride Prucalopride Tegaserod
Antispasmodics ²¹	Mebeverine Otilonium bromide Pinaverium bromide Tiropramide chloridrate Trimebutine	Mebeverine Otilonium bromide Pinaverium bromide Phloroglucinol Tiropramide hydrochloride Trimebutine Tiquizium bromide Combinations: Mebeverine + Simethicone Trimebutine + Simethicone	Hyoscine Dicyclomine Mebeverine Otilonium bromide Pinaverium bromide Propantheline	Butylhyoscine Dicyclomine Fenoverine Mebeverine Otilonium bromide Pinaverium bromide Peppermint Oil Trimebutine Combinations: Alverine + Simethicone Clebopride + Simethicone Pinaverium bromide + Simethicone
Tricyclics	Amitriptyline Imipramine Desipramine Nortryptilyne	*	Amitriptyline Imipramine Desipramine Nortryptilyne	Amitriptyline Imipramine Desipramine Nortryptilyne
SSRI's	Citalopram Fluoxetine Paroxetine Sertraline	*	Citalopram Fluoxetine Paroxetine Sertraline	Citalopram Fluoxetine Paroxetine Sertraline
Antidiarrheals	Cholestiramine Dyphenoxylate Loperamide	Glycopyrrolate Loperamide hydrochloride Ramosetron	Cholestiramine Dyphenoxylate Loperamide Ramosetron	Cholestiramine Loperamide Lidamidine
Antibiotics	Rifaximine Neomycin Paramomycin	Rifaximin	Rifaximin	Rifaximin
Probiotics				

Table 4 Continued

Medication	Italy	South Korea	India	Mexico
	Bacillus coagulans	Lactobacillus acidophilus	Lactobacillus	Bifidobacterium longum
	Bifidobacterium BB-12	Saccharomyces boulardii	Saccharomyces boulardii	W11
	Bifidobacterium infantis	Saccharomyces cerevisiae	VSL#3	Lactobacillus acidophilus
	Bifidobacterium longum E. Coli Nissle	VSL#3		Lactobacillus reuteri
	Geneffilus F-19			Saccharomyces boulardii
	Lactobacillus acidophilus			
	Lactobacillus casei DG			
	Lactobacillus paracasei			
	Lactobacillus reuteri			
	Lactobacillus rhamnosus			
	Saccharomyces boulardii			
	VSL#3			
Others			Simethicone	Simethicone

Although countries like Mexico (49, 50) and South Korea (53) have specific guidelines on approved medications for IBS, the current table includes medications not listed in these guidelines. *Not approved for IBS.

of these tests are relatively inexpensive (i.e., upper endoscopy: \$10–25 USD), another factor that facilitates their implementation. The study in Mumbai showed that patients with both dyspepsia and IBS underwent upper endoscopy (10%) more commonly than those with dyspepsia (3.6%) or IBS (1.3%) alone. The same was the case for abdominal ultrasound (15.5% vs 5.9% vs 1.3%).²⁶

The 2008 guidelines for IBS issued by the Mexican Gastroenterological Association recommended colonoscopy or barium enema together with flexible sigmoidoscopy, depending on availability, in patients older than 50 years of age or patients with alarm features regardless of age, to rule out colon cancer.³⁴ There is some evidence in favor of testing for parasite carriage in patients with IBS-D and further investigations are recommended in all patients whose symptoms persist after an initial treatment trial.³⁴ While testing for celiac disease is not recommended because of the prevalence of this condition in Mexico,⁴¹ 0.98% (CI 95%: 0.68–1.66),⁴² a more recent study in the state of Veracruz reported that 6.9% of IBS-Rome III patients (primarily IBS-D) vs 2.9% of controls, had either IgA anti-transglutaminase antibodies or IgA/IgG deamidated gliadin peptide antibodies.⁴³ Thus, further investigations are needed (Table 3).

WHICH MEDICATIONS ARE APPROVED AND AVAILABLE FOR FGIDS AND WHAT IS THE PROCESS OF REGISTRATION AND APPROVAL FOR NEW FGID DRUGS?

In Italy, among patients with uninvestigated dyspepsia, the most frequently prescribed medications were prokinetic drugs (50% of patients), antacids (40.4%),

proton pump inhibitors (PPIs; 15.6%), anxiolytics (8.7%), antispasmodics (8.4%), and histamine 2 receptors (H₂) blockers (4.4%; Table 4).³⁷ The high frequency of prokinetic drugs is related to the fact that they are licensed for the entire spectrum of dyspepsia. The study from Pisa showed that antispasmodics (40.4%) are the most commonly prescribed medications for IBS followed by probiotics (29.8%) and anxiolytics (20.4%). Patients with IBS-D received more prescriptions than those with IBS-C (91.4 vs 55.7%, $p = 0.001$).²³ In a more recent study among gastroenterologists, PPIs (42.2%) followed by antispasmodics (34.2%) were the most common treatments used by patients with FGIDs.⁴⁴ Approval of all medical treatments in the EU is regulated by the European Medicines Agency (EMA). Once approved, the product can be marketed in all EU countries.⁴⁵ In Italy, the Italian Agency for Drugs then decides whether the NHS should cover the product.⁴⁶ However, the NHS does not cover agents for the treatment of FGIDs, although PPIs, antidepressants, and cholestyramine, which are not licensed for FGIDs, are fully covered, so physicians prescribe them off-label for these conditions.

In South Korea, antidepressants are not approved for IBS (Table 4). Thus, to be able to prescribe these agents, physicians have to document a psychiatric diagnosis in their patients. The Korean Food & Drug Administration (KFDA) conducts the registration and approval of new medications for FGIDs. The KFDA has a Pharmaceutical and a Biopharmaceuticals and Herbal Safety Bureau. The former evaluates pharmaceutical products under the Gastroenterology and Metabolism Products Division, and is responsible for marketing authorization, clinical trials review, advertisement regulation, postmarketing surveillance, and quality control. In

Table 5 Characteristics and types of CAM

Country	Types of CAM	%	Source of recommendation	%
Italy*	Herbal products	36.7	Friends/colleagues	27.3
	Homeopathy	17.1	Herbalists	18.2
	Relaxation	5.5	GPs	17.5
	Acupuncture	3.5	Pharmacists	16.1
	Cognitive Behavioral Therapy	3.0	Homeopaths	6.3
	Dietary approaches:		Naturopaths	6.3
	• Empirical exclusion diets	39.7	Dieticians	5.6
	• Probiotics	31.7	Media	4.9
	• Prebiotics	22.6	Internet	2.8
	• Vitamin/minerals	5.0		
South Korea†	Over-the-counter products	8.1	No data	No data
	Health/functional foods	4.8		
	Folk remedies	8.8		
India‡	Homeopathy	No data	No data	No data
	Unani			
	Siddha			
	Ayurveda			
	Others:			
	• Faith healers			
	• Acupuncture			
	• Quacks			
	Herbal products	86.0	Friends	33.0
	Homeopathic remedies	15.0	Relatives	55.0
Acupuncture	9.0	Physicians	4.0	
Dietary approaches	44.0	Media	8.0	
Other:	5.0			
• Reflexology				
• Witchcraft				
• Magnet therapy				
• Aromatherapy				
• Human colostrum				
• Bull's gall.				

*Lahner *et al.*^{44,58} †Data modified from Choi *et al.*²⁹ ‡Personal communication from Ghoshal U from India. §Carmona-Sanchez *et al.*⁵⁸

terms of the drug approval evaluation process, their aim is to assure safety, efficacy, and quality of drug products used in the domestic market.⁴⁷

In India, 34% of IBS patients are treated with antidepressants (Table 4).⁴⁸ However, in a study in tertiary care in which 79.9% of the IBS patients and 34.3% of controls had psychiatric comorbidities, only 7.6% of the IBS patients were receiving specific medications for them.⁴⁹ All new medications have to be approved by the Ministry of Health's Central Drugs Standard Control Organization. Applications are evaluated by groups of experts and approval is based on the scientific merit of the drugs based on data generated within India and abroad.⁵⁰

In Mexico, the IBS guidelines of the Health Secretariat recommends medications such as butylhyoscine, mebeverine, metamizol, acetaminophen, as well as selective serotonin reuptake inhibitors, tricyclic antidepressants, fiber supplements, and osmotic laxatives.⁵¹ While these recommendations may be followed in public hospitals and social security systems, specific medications are not always available at the different institutions. There are also evidence-

based guidelines from the Mexican Gastroenterological Association that are usually followed by gastroenterologists but not necessarily by other specialists or GPs (Table 4).⁵² The process of approval of 'new molecules' is regulated by the *Comisión Federal para la Protección Contra Riesgos Sanitarios* (Federal Commission for the Protection Against Sanitary Risks: COFEPRIS). A new molecule is defined as one that has not been previously used in the country or registered elsewhere, for which there is limited clinical experience and/or controversial data, includes a combination of two or more active components not available in Mexico, or is available in the country but registration is requested for a new indication. In any of the above, the COFEPRIS convenes a meeting of the Committee for New Molecules that includes COFEPRIS's High Commissioner, the agency's Director of Pharmaco-vigilance, representatives of the government's health authorities, industry, academic societies, and of the National Academy of Medicine. This committee makes recommendations regarding the safety, efficacy, and quality of the new product, as well as its commercial feasibility.⁵³

USE OF CAM FOR FGIDS

In Italy, in 2011, a survey among a randomly selected group of gastroenterologists^{44,54} showed that 48.7% of FGID patients used CAM during the previous year, while 64.3% used dietary modification and/or supplementation (Table 5). Female gender (OR 2.4, 95% CI 1.1–5.5) and lower abdominal symptoms (OR 9.1, 95% CI 3.8–21.6) were significantly associated with the use of CAM. In most cases, it complemented conventional treatment, which was used by 81.4% of FGID patients. Those with comorbidities were more likely to use more than one treatment option (e.g., conventional, diet, and CAM). The use of CAM was motivated by the belief that it is natural (39.9%), safe (34.3%), makes patients feel better (14.7%), and is more gentle (11.2%) than conventional drugs.⁵⁴

In South Korea, the results of a study among 273 patients with IBS showed that one-third of them used alternative options including over-the-counter medications (8.1%), functional health foods such as probiotics and prebiotics (8.4%), health aid tools such as hot packs (4.8%), and folk remedies (8.8%) (Table 5). IBS patients consulted on average 1.9 ± 1.3 times a year (range: 1–6) at Oriental medicine clinics.²⁴

In India, there are several alternative medicine systems. Some are very popular, especially as they are less expensive than modern allopathic medicine and widely available even in remote rural areas, and some even have teaching and training schools, such as homeopathy and Ayurveda (Table 5).

In Mexico, one study has addressed the use of CAM (Table 5) among 413 patients (IBS: 61%, functional dyspepsia: 22%, GERD: 7%), showing that CAM was more frequently used in IBS than the others (51% vs 36 vs 27%, respectively).⁵⁵ Predictors of CAM were prior abdominal surgery, IBS, more than three consultations with physicians over the previous year, emergency room visits, sick leave because of FGIDs, and a history of taking benzodiazepines.

WHAT IS THE OVERALL HEALTHCARE BURDEN OF THE FGIDS?

A recent systematic review on the burden of illness of IBS-C in Europe found no studies on the cost of illness or use of diagnostic resources in Italy.⁵⁶ In contrast, one study showed that compared to controls, IBS-C patients reported 108% and 71% more consultations to general practice and specialists, respectively.⁵⁷ There is almost no information on expenses incurred in treating FGIDs. One survey indicated that the mean annual cost for a diagnostic work-up for IBS was \$85.7 USD

and the *indirect* costs incurred by patients with functional constipation was \$5100 USD.⁵⁸

In South Korea, the National Evidence-based Healthcare Collaboration Agency estimated that the number of outpatient visits per year by IBS patients is 2.5 ± 4.0 and the number of days of hospital stay for inpatients with IBS is 14.7 ± 25.0 . Diagnostic tests are frequently repeated, for example, colonoscopy 1.5 times on average, sigmoidoscopy 1.2, and abdominal ultrasound 1.6 times.⁴⁰ Direct costs because of IBS were estimated at \$383 million USD in 2008. According to data, claims from the Health Insurance Reviews and Assessment Service, expenditures for healthcare and pharmacy services were \$300 million USD, and \$77.4 million for transportation. If indirect costs such as those incurred by over-the-counter medications, health foods, and productivity losses were added, total expenditures for IBS were estimated at \$484–557 million USD. In addition, reimbursements for IBS during the same year were estimated at \$154 million USD, which corresponded to 0.46% of total reimbursements for the entire population of South Korea. These included expenses in healthcare institutions, copayments, and uncovered costs for consultation fees, diagnostic procedures (i.e., laboratory tests, imaging examinations), therapeutic procedures, and fees for inpatient and outpatient care.⁵⁹ The average annual NHI costs per IBS patient was estimated at \$64.1 USD; \$43.7 per outpatient visit and \$1087.9 per admission. Individual NHI expenses were lower for women than for men with IBS (\$60.8 vs \$68.6). Medical expenses were also higher for 40–59-year-old patients followed by those older than 60 years and then 30–39-year olds. Furthermore, the mean cost per IBS patient was almost five times higher in teaching hospitals than in primary care clinics. However, within the NHI, total expenses for IBS were higher in primary care clinics ($\$68.2 \times 10^6$ USD) followed by general hospitals ($\$44.9 \times 10^6$) and teaching hospitals ($\$14.0 \times 10^6$).^{25,40,59}

In India, public spending on healthcare has gradually increased from 0.22% of the public budget in 1950–51 to 1.05% in 1980s and 0.90% since then. Expenditures per capita increased from 1 Indian Rupee in 1950–51 to 215 in 2003–04 (\$3.90 USD),¹⁷ which is still very low. There is no information on expenditures related to FGIDs. In terms of medications, most available drugs are generic or specially priced for the Indian market, so the cost of most drugs is low. For example, one course of ranitidine or famotidine for 10 days costs \$0.04–0.05 USD, while 10 capsules of the probiotic VSL#3 can cost as much as \$4.50. Antispasmodics can vary from \$0.90 USD for 10 tablets or capsules (i.e., clidinium bromide, hyoscine) to \$14.40 for 10 capsules of pinaverium

bromide. Work absenteeism has been reported at 8.7 ± 12.7 weeks a year among IBS-Rome III patients from a tertiary care center in New Delhi.

In Mexico, according to World Review 2012,¹⁹ the government covers only 48% of total spending on healthcare, while 70% of the cost of medications is covered by patients themselves. Mexico also represented the second largest market for pharmaceutical sales in Latin America being more than \$15.8 billion USD at the end of 2011. Indirect data from a retrospective study of IBS-Rome I patients at an academic referral center in Mexico City, showed that over 33.4 (range: 1–243) months of follow-up, a median of 22.4 (1–82) diagnostic studies were ordered per patient; 5 (1–11) before the diagnosis of IBS was established and 17.4 (1–18) later, even though IBS was diagnosed during the first visit in 87% of the cases.⁶⁰ Some of the tests, such as blood chemistry panel, were ordered up to 18 times during follow-up.⁶⁰ A follow-up paper concluded that if diagnostic guidelines had been followed,⁴¹ costs could have been reduced by 90%.⁶¹ More recently, as part of a nationwide clinical trial, a monthly mean cost of \$107 USD was estimated per IBS patient, independently of IBS-subtype.⁶² Expenses included endoscopy and imaging ($\$224 \pm 25$ USD), prescribed medications ($\$152 \pm 11$), medical visits ($\138 ± 10), laboratory work-up ($\$106 \pm 10$), and transportation ($\22 ± 3). It should be noted that 52% of the patients in this study earned less than \$500 USD per month.⁶² In addition, 80% of the patients reported absenteeism ranging from 1 to 8 h/week, while presenteeism was reported by almost 91% of the patients and was more common among IBS-D (33%) vs IBS-C (13%) and IBS-M (16%).⁶³

SUMMARY AND CONCLUSIONS

In summary, while Italy and South Korea have effective universal health care coverage, India and Mexico have universal coverage only in theory. Many people at the lower extreme of the socioeconomic spectrum do not receive good healthcare, others choose not to use it, and some are not able to access it. These differences may impact the care of patients with FGIDs. The majority of patients with IBS appear to be cared for in primary care, but healthcare service and providers differ across areas, with great differences in the availability and use of diagnostic tools as well as specialist-based treatments. Referrals to higher levels of care are common, but limited by available resources and the extent of knowledge and experience in the management of FGIDs by GPs. In addition, in places like India and Mexico, more affluent patients have access to higher levels of care and private practice, with better quality of care.

Rome diagnostic criteria, in Italy, Mexico, and South Korea, are well accepted and gastroenterologists are familiar with them. Yet, it appears that non-specialists such as GPs in Italy do not use the Rome criteria in their clinical practice. Physicians in India do not feel that Rome criteria are relevant to their practice as they perceive a disconnect between the criteria and their patients' report of symptoms, as pain and discomfort are absent in a third of patients and stool frequency does not differ between those with diarrhea- and constipation-predominant IBS.

Laboratory and endoscopic investigations in IBS patients are primarily driven by the need to rule out colon cancer. In addition, there are regional differences based on local disease prevalence, such as celiac disease in Italy, dyspepsia and *Helicobacter pylori* in India and South Korea, or parasitic infections in Mexico. Furthermore, the low cost of endoscopy in places like Italy and India appears to make it widely accepted as a first-line investigation.

Treatments that appear to be universally available and regularly prescribed in the four countries analyzed are antispasmodics, osmotic agents, and laxatives. Other treatments, especially newer agents vary according to local regulatory policies, or because of economic cost. In some countries, data from clinical trials conducted in other countries can facilitate the approval process, but additional local clinical trials are usually requested. CAM is used in all four countries, especially in India where there are training schools in the field. In Italy, patients use them in addition to conventional therapy. However, physicians in western societies should become more familiar with the various types of CAM, their effectiveness, and side effects. Scientific research and well-controlled clinical trials are also warranted to gain a better understanding of the mechanistic basis, efficacy, and safety of CAM therapies.

Finally, there are differences in the healthcare burden of FGIDs. For example, in Italy medications for FGIDs are not covered by public healthcare services. In India and Mexico, public spending on healthcare is inadequate, impacting on the diagnosis and management of these patients. Therefore, in both of these countries, the majority of spending comes directly from patient out-of-pocket expenditure. In contrast, all expenses for FGIDs are covered to a greater extent by the public healthcare system in South Korea.

This report provides examples, some well documented and some derived from personal experience and expertise, of a number of crucial aspects of health care of FGIDs. It represents part of the Rome Foundation's comprehensive global initiative to foster multinational research in FGIDs and the related

Table 6 Pitfalls and future directions of cross-cultural healthcare comparisons in FGIDs as identified by the Rome Foundation Multinational Working Team

Pitfalls	Future directions
1. Healthcare systems differ across countries.	It is important to ensure that patients are recruited from similar and comparable systems, and have comparable educational and socioeconomic status.
2. Patients with FGIDs receive healthcare in different levels (i.e., primary, secondary, or tertiary) across countries. Thus, patients from primary care in one country may have similar disease severity to patients from tertiary care in another country.	The complexity and severity of FGIDs across study groups must be similar based on instruments designed for this purpose and not based on the level of care in which they are taken care of.
3. Knowledge and use of Rome criteria is limited especially among GPs and Rome criteria may not be applicable in every culture.	Educational activities are needed to spread the knowledge of the different versions of the Rome Criteria and the diagnoses of the different FGIDs. In addition, the criteria themselves or the Rome Diagnostic Questionnaires must be translated and validated into the different languages and countries where the study will be conducted and validated against the local available criteria assuring that patients are comparable.
4. Diagnostic investigations also vary across countries based on availability and costs.	Recruited patients need to be investigated with the same diagnostic procedures to rule out organic or comorbid disorders.
5. Available and approved medications for FGIDs vary across the world and healthcare systems.	When considering 'refractory' patients as inclusion criteria in a research study (i.e., clinical trial) refractoriness must be to the exact same type of therapies (i.e., antispasmodics: describe exactly which ones).
6. While CAM is used across countries, therapies classified under this label vary across them. In addition, controlled trials to determine their efficacy and mechanistic studies are lacking.	Studies comparing available CAM options, their indications, and source of recommendation, need to be investigated across countries and cultures. In addition, well-designed controlled trials are warranted to determine their efficacy and safety as well as investigations to determine their mechanistic effect.
7. The economic burden of IBS varies considerably across countries and healthcare systems.	When analyzing the economic burden of any FGID, costs should be compared in terms of the proportion to public budgets, expenditures per capita, personal income, etc. and not in absolute values.

methodological issues. By comparing four different countries, it is clear that there are regional differences that may be related to socioeconomic and cultural factors. Nonetheless, the current analysis is not sufficient to draw general conclusions applicable worldwide, nor was it intended to be. A truly global assessment is impossible because of the absence of any data from several regions and countries. However, this type of analysis may provide directions for improving standards of care of FGIDs around the globe, and points to the need for further research in this area. Finally, when conducting cross-cultural and multinational research in FGIDs, the issues reviewed herein should be included in the studied populations. Table 6 describes pitfalls and future directions of cross-cultural healthcare comparisons in FGIDs.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

MS conceptualized the study, collected information, drafted the manuscript, and approved the final draft; ESC collected information, helped edit the manuscript, and approved the final draft; UCG collected information, helped edit the manuscript, and approved the final draft; S-JM collected information, helped edit

the manuscript, and approved the final draft; CDG helped edit the manuscript and approved the final version; EQ helped edit the manuscript and approved the final version; K-AG conceptualized

the study, helped edit the manuscript, and approved the final draft; AS conceptualized the study, helped edit the manuscript, and approved the final draft.

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